Exhibit D

Centers for Disease Control and Prevention

COVID-19

Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19)

Updated Dec. 8, 2020 Print

Influenza and SARS-CoV-2

When SARS-CoV-2 and influenza viruses are co-circulating, clinicians should consider both viruses, as well as co-infection, in patients with acute respiratory illness symptoms because of similar signs and symptoms. Testing and treatment guidance in priority groups is available. For more information on influenza and Covid-19 see the NIH Treatment Guidelines .

Summary of Recent Changes

Updates as of November 3, 2020

As of November 3, 2020

- New information for Laboratory and Radiographic Findings
- New information for Pediatric Considerations
- Revisions for clarity and significant updates to footnotes throughout
- Influenza alert box
- Information on FDA approval of remdesivir

View Previous Updates

This document provides guidance on caring for patients infected with SARS-CoV-2, the virus that causes COVID-19. The National Institutes of Health (NIH) have published guidelines for the clinical management of COVID-19 prepared by the COVID-19 Treatment Guidelines Panel. The recommendations are based on scientific evidence and expert opinion and are regularly updated as more data become available.

For guidance related to children with COVID-19, please see the Pediatric Considerations section below.

Clinical Presentation

Incubation period

The incubation period for COVID-19 is thought to extend to 14 days, with a median time of 4-5 days from exposure to symptoms onset.[1-3] One study reported that 97.5% of people with COVID-19 who have symptoms will do so within 11.5 days of SARS-CoV-2 infection.[3]

Presentation

The signs and symptoms of COVID-19 present at illness onset vary, but over the course of the disease many people with COVID-19 will experience the following:[1,4-9]

- Fever or chills
- Cough
- Shortness of breath or difficulty breathing
- Fatigue
- Muscle or body aches
- Headache
- New loss of taste or smell
- Sore throat
- Congestion or runny nose
- Nausea or vomiting
- Diarrhea

Symptoms may differ with severity of disease. For example, shortness of breath is more commonly reported among people who are hospitalized with COVID-19 than among people with milder disease (non-hospitalized patients).[10, 11] Atypical presentations of COVID-19 occur often, and older adults and people with medical comorbidities may experience fever and respiratory symptoms later during the course of illness than people who are younger or who do not have comorbidities.[12, 13] In one study of 1,099 hospitalized patients, fever was present in only 44% at hospital admission but eventually 89% of patients had a fever sometime during hospitalization.[1] Fatigue, headache, and muscle aches (myalgia) are among the most commonly reported symptoms in people who are not hospitalized, and sore throat and nasal congestion or runny nose (rhinorrhea) also may be prominent symptoms. Many people with COVID-19 experience gastrointestinal symptoms such as nausea, vomiting or diarrhea, sometimes prior to having fever and lower respiratory tract signs and symptoms.[9] Loss of smell (anosmia) or taste (ageusia) has been commonly reported, in a third of patients in one study, especially among women and younger or middle-aged patients.[14]

Asymptomatic and Presymptomatic Infection

Several studies have documented infection with SARS-CoV-2, the virus causing COVID-19, in patients who never have symptoms (asymptomatic) and in patients not yet symptomatic (presymptomatic).[15-29] Since people who are asymptomatic are not always tested, the prevalence of asymptomatic infection and detection of presymptomatic infection is not yet well understood. Current data, based on reverse transcription-polymerase chain reaction (RT-PCR) testing for SARS-CoV-2 and on serologic studies, suggest asymptomatic infections can be common and that the total number of infections is likely greater than the number of cases reported.[15,22-24,30,31] Patients may have abnormalities on chest imaging before the onset of symptoms.[16]

Asymptomatic and Presymptomatic Transmission

Increasing numbers of epidemiologic studies have documented SARS-CoV-2 transmission during the presymptomatic incubation period.[19,28,29,32] Studies using RT-PCR detection have reported low cycle thresholds, indicating larger quantities of viral RNA, among people with asymptomatic and presymptomatic SARS-CoV-2 infection. Likewise in viral culture, viral growth has been observed in specimens obtained from patients with asymptomatic and presymptomatic infection.[22,24,27,33] The proportion of SARS-CoV-2 transmission due to asymptomatic or presymptomatic infection compared with symptomatic infection is not entirely clear; however, recent studies do suggest that people who are not showing symptoms may transmit the virus.[22,24,34]

Clinical Course

Illness Severity

The largest cohort reported to date, including more than 44,000 people with COVID-19 from China, showed that illness severity can range from mild to critical:[35]

- Mild to moderate (mild symptoms up to mild pneumonia): 81%
- Severe (dyspnea, hypoxia, or more than 50% lung involvement on imaging): 14%
- Critical (respiratory failure, shock, or multiorgan system dysfunction): 5%

In this study, all deaths occurred among patients with critical illness, and the overall case fatality ratio (CFR) was 2.3%.[35] The CFR among patients with critical disease was 49%.[35] Among children in China, illness severity was lower than in adults, with 94% of affected children having asymptomatic, mild, or moderate disease; 5% having severe disease; and less than 1% having critical disease.[13] Among U.S. COVID-19 cases reported January 22–May 30, 2020, overall the proportion of people who were hospitalized was 14%, including 2% admitted to the intensive care unit (ICU). Overall 5% of patients died.[36]

Clinical Progression

Among patients in multiple early studies from Wuhan, China who had severe COVID-19 illness, the median time from their onset of illness to the time they experienced dyspnea was 5–8 days; the median time from onset of illness to acute respiratory distress syndrome (ARDS) was 8–12 days; and the median time from onset of illness to ICU admission was 9.5–12 days.[5,6,37,38] Clinicians should be aware of the potential for some patients with COVID-19 to rapidly deteriorate about one week after illness onset. Among all hospitalized patients, 26%–32% of patients were admitted to the ICU.[6,8,38] Among all patients, 3%–17% had ARDS compared with 20%–42% for hospitalized patients and 67%–85% for patients admitted to the ICU.[1,4-6,8,38] Mortality among patients admitted to the ICU ranged from 39% to 72% depending on the study and characteristics of patient population.[5,8,37,38] The median length of hospitalization among survivors was 10–13 days.[1,6,8]

Risk Factors for Severe Illness

Age is a strong risk factor for severe illness, complications, and death.[1,6,8,13,34,35,39-42] Among the cohort of more than 44,000 confirmed cases of COVID-19 in China, the CFR increased with advancing age, and was highest among the oldest cohort. Mortality among people 80 years and older was 14.8%; 70–79 years, 8.0%; 60–69 years, 3.6%; 50–59 years, 1.3%; 40–49 years, 0.4%; and for those younger than 40 years, 0.2%.[35] Based on U.S. epidemiologic data through March 16, 2020, CFR was highest in people aged 85 years or older (range 10%–27%), followed by people aged 65–84 years (3%–11%), aged 55–64 years (1%–3%), and was lower in people younger than 55 years (<1%).[39]

CFR in the large cohort in China was elevated for patients with comorbidities, with 10.5% of those with underlying cardiovascular disease, 7.3% of those with diabetes, 6.3% of those with chronic respiratory disease, and 5.6% of those with cancer dying of COVID-related illness.[35] Prior stroke, diabetes, chronic lung disease, and chronic kidney disease have all been associated with increased illness severity and adverse outcomes due to COVID-19. Heart conditions, including heart failure, coronary artery disease, cardiomyopathies, and pulmonary hypertension, put people at higher risk for severe illness from COVID-19. People with hypertension may be at an increased risk for severe illness from COVID-19 and should continue to take their medications as prescribed. [43]

Accounting for differences in age and prevalence of underlying conditions, the mortality associated with COVID-19 that has been reported in the United States appears similar to reports from China.[36, 39] See People Who Are at Increased Risk for Severe Illness to learn more about who is at increased risk.

Reinfection

To date, limited data exist about reinfection with SARS-CoV-2 after recovery from COVID-19.[44-46] Published case reports have shown that reinfection is possible, but it is still unclear how long people who have recovered from COVID-19 are protected against reinfection with SARS-CoV-2, what concentration of antibodies is needed to confer protection, and how often reinfection may occur.[44-46]

While viral RNA shedding declines with resolution of symptoms, SARS-CoV-2 RNA shedding may continue for days to weeks.[37,47,48] Thus, detection of viral RNA during convalescence does not necessarily indicate replication-competent virus (infectiousness) or the presence of new infectious virus. Clinical infection has been correlated with the detection of IgM and IgG antibodies.[48-51] People who have recovered can continue to shed detectable SARS-CoV-2 RNA in upper respiratory specimens for up to 3 months after illness onset, albeit at concentrations considerably lower than during illness, in ranges where replication-competent virus has not been reliably recovered and infectiousness is unlikely. For more information about duration of viral shedding among people with SARS-CoV-2 infection, see Duration of Isolation and Precautions for Adults with COVID-19. Also see CDC's Investigative Criteria for Suspected Cases of SARS-CoV-2 Reinfection as well as the Common Investigation Protocol for Investigating Suspected SARS-CoV-2 Reinfection.

Laboratory and Radiographic Findings

Testing for Infection

Diagnosis of COVID-19 requires detection of SARS-CoV-2 RNA by RT-PCR. Detection of SARS-CoV-2 viral RNA is better in nasopharynx samples compared with throat samples.[32,47,52] Lower respiratory samples may have better viral yield than upper respiratory samples.[53] SARS-CoV-2 antigen tests can also be used in a variety of testing strategies. See Interim Guidance for Rapid Antigen Testing for SARS-CoV-2 for more information about the effective use of antigen tests in different testing situations. SARS-CoV-2 RNA has also been detected in stool and blood.[51,54] Detection of SARS-CoV-2 RNA in blood may be a marker of severe illness.[55]

Infection with both SARS-CoV-2 and with other respiratory viruses (e.g., influenza) or bacteria is well documented, and detection of another respiratory pathogen does not rule out COVID-19.[56] Clinicians are encouraged to consider testing for other viral causes of respiratory illness, for example influenza, in addition to testing for SARS-CoV-2 depending on patient age, season, or clinical setting. Clinicians should also consider bacterial and fungal causes of pneumonia (e.g. Legionnaires' disease in patients exposed to water from previously closed buildings or overnight travel, pneumococcal pneumonia, and coccidioidomycosis) in patients who are PCR-negative for SARS CoV-2, as clinically indicated. See IDSA/ATS guidelines .

For more information about COVID-19 testing and specimen collection, handling and storage, visit Overview of Testing for SARS-CoV-2 (COVID-19) and Frequently Asked Questions about COVID-19 for Laboratories.

Other Laboratory Findings

Lymphopenia is the most common laboratory finding among people with COVID-19, and is found in up to 83% of hospitalized patients.[1,5] Lymphopenia, neutrophilia, elevated serum alanine aminotransferase and aspartate aminotransferase levels, elevated lactate dehydrogenase, high C-reactive protein (CRP), and high ferritin levels may be associated with greater illness severity.[1,5,6,8] Elevated D-dimer and lymphopenia have been associated with mortality.[8,37,57,58] Procalcitonin is typically normal on admission, but may increase among those patients admitted to an ICU.[4-6] Patients with critical illness had high plasma levels of inflammatory makers, suggesting potential immune dysregulation.[5,59]

Radiographic Findings

Chest radiographs of patients with COVID-19 typically demonstrate bilateral air-space consolidation, although some patients have unremarkable chest radiographs early in the disease.[1,47] Chest Computerized Tomography (CT) images from patients with COVID-19 typically demonstrate bilateral, peripheral ground glass opacities.[60-71] Because this chest CT imaging pattern is non-specific and can be found in pneumonias caused by other infections, the diagnostic value of chest CT imaging for COVID-19 may be low and dependent upon radiographic interpretation.[70] One study found that 56% of patients who presented within two days of diagnosis had a normal CT.[62] Conversely, other studies have identified chest CT abnormalities in patients prior to the detection of SARS-CoV-2 RNA in RT-PCR testing of nasopharyngeal samples.[71] Given the variability in chest imaging findings, chest radiograph or CT alone is not recommended for the diagnosis of COVID-19. The American College of Radiology also does not recommend CT for screening, or as a first-line test for diagnosis of COVID-19. (See American College of Radiology Recommendations).

Clinical Management and Treatment

The National Institutes of Health (NIH) published guidelines on prophylaxis use, testing, and management of patients with COVID-19. For more information, please visit the NIH Coronavirus Disease 2019 (COVID-19) Treatment Guidelines . The recommendations are based on scientific evidence and expert opinion and are regularly updated as more data become available. The U.S. Food and Drug Administration (FDA) has approved one drug remdesivir (Veklury) for the treatment of COVID-19 in certain situations. Clinical management of COVID-19 includes infection prevention and control measures and supportive care, including supplemental oxygen and mechanical ventilatory support when indicated.

Mild to Moderate Disease

Patients with a mild clinical presentation (absence of viral pneumonia and hypoxia) may not initially require hospitalization, and most patients will be able to manage their illness at home. The decision to monitor a patient in the inpatient or outpatient setting should be made on a case-by-case basis. This decision will depend on the clinical presentation,

requirement for supportive care, potential risk factors for severe disease, and the ability of the patient to self-isolate at home. Patients with risk factors for severe illness (see People Who Are at an Increased Risk for Severe Illness) should be monitored closely given the possible risk of progression to severe illness, especially in the second week after symptom onset.[5,6,35]

For information regarding infection prevention and control recommendations, please see Infection Control Guidance for Healthcare Professionals about Coronavirus (COVID-19).

Severe Disease

Some patients with COVID-19 will have severe disease requiring hospitalization for management. Inpatient management includes supportive management of the most common complications of severe COVID-19: pneumonia, hypoxemic respiratory failure/ARDS, sepsis and septic shock, cardiomyopathy and arrhythmia, acute kidney injury, and complications from prolonged hospitalization, including secondary bacterial and fungal infections, thromboembolism, gastrointestinal bleeding, and critical illness polyneuropathy/myopathy.[1,4-6,13,35,40,72-74]

More information can be found at Clinical Questions about COVID-19: Questions and Answers. Additional resources and guidance documents on the treatment and management of COVID-19, including inpatient management of critically ill patients, are provided below.

Hypercoagulability and COVID-19

Some patients with COVID-19 may have signs of a hypercoagulable state and be at increased risk for venous and arterial thrombosis of large and small vessels.[57,58,75-80] Laboratory abnormalities commonly observed among hospitalized patients with COVID-19-associated coagulopathy include:

- Mild thrombocytopenia
- Increased D-dimer levels
- Increased fibrin degradation products
- Prolonged prothrombin time

Elevated D-dimer levels have been strongly associated with greater risk of death.[8,37,57,58]

There are several reports of hospitalized patients with thrombotic complications, most frequently deep venous thrombosis and pulmonary embolism.[58,75-77] Other reported manifestations include:

- Microvascular thrombosis of the toes (“COVID toes”)
- Clotting of intra-vascular catheters
- Myocardial injury with ST-segment elevation
- Large vessel strokes[78,79]

The pathogenesis for COVID-19-associated hypercoagulability remains unknown. However, hypoxia and systemic inflammation secondary to COVID-19 may lead to high levels of inflammatory cytokines and activation of the coagulation pathway.[81]

Data available to inform clinical management around prophylaxis or treatment of venous thromboembolism in COVID-19 patients are still evolving, with new information released often. Several national professional associations provide resources for up-to-date information concerning COVID-19-associated hypercoagulability, including management of anticoagulation. More information on hypercoagulability and COVID-19 is available from the American Society of Hematology and National Institutes of Health.

Pediatric Considerations

Increasingly, data indicate that the clinical symptoms experienced by children with COVID-19 are similar to adults, but disease is usually milder than adults and severity of symptoms varies by age of the child. Many children infected with SARS-CoV-2 remain asymptomatic or have mild illness.[82,83] Commonly reported symptoms in children with COVID-19 include cough or fever, and many children also experience gastrointestinal or other symptoms.[84-88] Even though most children with COVID-19

have asymptomatic or mild illness, severe outcomes, including deaths, have been reported in children.[89] Children of all ages with certain underlying medical conditions may be at increased risk of severe illness; also infants (<12 months of age) may be at increased risk for severe illness from COVID-19.[89, 90]

CDC and partners are investigating the multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19. Patients with MIS-C usually present with persistent fever, abdominal pain, vomiting, diarrhea, skin rash, mucocutaneous lesions and, in severe cases, hypotension and shock. Affected children have elevated laboratory markers of inflammation (e.g., CRP, ferritin), and a majority of patients have laboratory markers of damage to the heart (e.g., troponin; B-type natriuretic peptide (BNP) or proBNP). Some patients have myocarditis, cardiac dysfunction, and acute kidney injury. Not all children with MIS-C experience the same signs and symptoms, and some children may have symptoms not listed here. MIS-C may begin weeks after a child was infected with SARS-CoV-2. The child might have been infected from an asymptomatic contact and, in some cases, the child and their caregivers might not realize that the child had been infected.

For expanded considerations on the care of children with confirmed or suspected COVID-19 and associated complications, refer to:

- Information for Pediatric Healthcare Providers
- Evaluation and Management Considerations for Neonates At Risk for COVID-19
- Information for Healthcare Providers Caring for Breastfeeding Women
- Information for Obstetric Healthcare Providers
- Information for Healthcare Providers about Multisystem Inflammatory Syndrome in Children (MIS-C)
- Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children .

Investigational Therapeutics

The National Institutes of Health have published guidelines for the medical management of COVID-19 prepared by the COVID-19 Treatment Guidelines Panel. These guidelines contain information about therapeutics and will be updated as new information emerges and drugs and other therapeutic interventions are approved for use by FDA. Persons seeking information about registered clinical trials for COVID-19 in the United States can search for such information here: ClinicalTrials.gov .

Discontinuation of Transmission-Based Precautions or Home Isolation

Patients who have clinically recovered and are able to discharge from the hospital, but who have not been cleared from their Transmission-Based Precautions, can continue isolation at their place of residence until cleared. For recommendations on discontinuation of Transmission-Based Precautions or home isolation for patients who have recovered from COVID-19, see:

- Interim Guidance for Discontinuation of Transmission-Based Precautions and Disposition of Hospitalized Patients with COVID-19
- Interim Guidance for Discontinuation of Isolation for Persons with COVID-19 Not in Healthcare Settings

Previous Updates

Updates from Previous Content

As of October 27, 2020

- Updated content to Reinfection

As of September 10, 2020

- Updated content to Reinfection

As of June 20, 2020, to reflect the following:

- Updated content to Clinical Presentation
- Refer to People Who Are at Increased Risk for Severe Illness
- New information about Reinfection
- New information about Therapeutics
- Minor revisions for clarity and updates to footnotes throughout

As of May 29, 2020

- Refer to updated symptoms of Coronavirus

As of May 25, 2020

- Refer to new multisystem inflammatory syndrome in children (MIS-C) guidance for healthcare providers

As of May 20, 2020

- Refer to new guidance for Evaluation and Management Considerations for Neonates At Risk for COVID-19

As of May 12, 2020

- New information about COVID-19-Associated Hypercoagulability
- Updated content and resources to include new NIH Treatment Guidelines
- Minor revisions for clarity

CDC Resources

- Healthcare Professionals: Frequently Asked Questions and Answers
- Information for Pediatric Healthcare Providers
- Evaluating and Testing Persons for Coronavirus Disease 2019 (COVID-19)
- Frequently Asked Questions on COVID-19 Testing at Laboratories
- Infection Control Guidance for Healthcare Professionals about COVID-19
- Interim Infection Prevention and Control Recommendations for Patients with Suspected or Confirmed Coronavirus Disease 2019 (COVID-19) or in Healthcare Settings
- Evaluation and Management Considerations for Neonates At Risk for COVID-19
- COVIDView: A Weekly Surveillance Summary of U.S. COVID-19 Activity

Additional resources

- World Health Organization. Interim Guidance on Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected
- Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19)
- Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016
- Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children
- Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America

- ACR Recommendations for the use of Chest Radiography and Computed Tomography (CT) for Suspected COVID-19 Infection
- National Institutes of Health: Coronavirus Disease 2019 (COVID-19) Treatment Guidelines
- Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19 Infection

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